Two-Year Longitudinal Changes in Lower Limb Strength and Its Relation to Loss in Function in a Large Cohort of Patients With Duchenne Muscular Dystrophy

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Objective: The main objective of this study was to examine the effect of disease on strength in two functionally important lower limb muscles for a period of 2 yrs in children with Duchene muscular dystrophy.

Design: Seventy-seven Duchene muscular dystrophy children participated in this study. Plantar flexors, knee extensors, strength, and performance on timed tests (6-min walk, 4-stairs, 10-m walk, supine-up) were assessed yearly for 2 yrs. Multivariate normal regression was used to assess changes in strength over time in the Duchene muscular dystrophy group. Spearman correlations were computed to examine relationship between strength and function.

Results: Normalized plantar flexor and knee extensor strength showed a significant decrease ($P < 0.05$) over 2 yrs, with larger declines in knee extensor. At baseline, knee extensor strongly correlated with performance on timed tests. However, plantar flexor strength was found to be a stronger predictor of *loss* in ambulatory function. Modest correlations ($r = 0.19$–0.34) were found between the decline in strength and functional performance over 2 yrs.

Conclusions: This study describes the loss of lower limb strength in a large cohort of Duchene muscular dystrophy children for 2 yrs. The findings support that lower limb strength alone cannot account for the decline in performance on functional tests, and the role of other contributing factors, such as compensatory strategies, should be considered.

Key Words: Duchenne Muscular Dystrophy, Strength, Function, Quantitative Myometry

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Duchenne muscular dystrophy (DMD) is characterized by the progressive loss of skeletal muscle strength with children losing the ability to ambulate by 10 to 15 yrs of age.[1,2] Individuals affected by DMD usually pass away in the third decade of life because of cardiopulmonary and/or respiratory complications.[3,4] Even though DMD is a neuromuscular disorder characterized by a typical pattern of progression, a great degree of variability has been observed between patients in terms of strength and functional ability.[5]

At present, there is no cure for DMD.[6] Various therapeutic strategies including exon skipping[7] and gene therapy[8] are being pursued and moving through the different phases of development. These interventions are intended to ameliorate the disease pathology to improve muscle quality and increase functional ability as well as overall quality of life. Currently, glucocorticosteroids, noninvasive ventilatory support, cardioprotective, and physical therapy management are considered the standard of care and have demonstrated a positive effect on strength, functional ability, pulmonary/cardiac functions, and a delay in the development of physical disabilities.[6,9]

Because the primary goal of current treatments is to maintain (if not improve) muscle strength and functional ability, changes in these functional measures have been used as end

points to understand the natural disease progression and evaluate therapeutic efficacy of various treatments.[1,5,10] A variety of strength and functional tests has been used in both natural history studies[1,5,10,11] and clinical trials.[7,12] Quantitative myometry is one of the more sensitive and reliable methods for examining force production of specific muscle groups and has been used in cross-sectional and longitudinal studies.[1,5,10,13] To our knowledge, no study has compared the loss of force production in proximal and distal lower limb muscle groups using quantitative myometry in children with DMD and examined its relationship to decline in functional ability.

The primary objective of this study was to examine the decline in muscle strength in proximal and distal leg muscle groups in a large cohort of children with DMD. We specifically examined the proximal knee extensors (KE) and distal plantar flexors (PF), given their important role in stair climbing and walking for 2 yrs. Furthermore, to elucidate the role of lower extremity muscle strength in the decline of functional ability, we also investigated the relationships between decline in lower limb strength and performance on ambulatory functional tests. Finally, we explored the ability of KE and PF strength to predict the loss of the ability to perform specific timed performance tests.

METHODS

This study was conducted as part of a multicenter natural history study, referred to as imaging DMD. Data on 77 children with DMD who had participated in the imaging DMD study for 2 yrs and 46 control healthy individuals were analyzed for this study. Patients included had a confirmed diagnosis of DMD based on genetic report, with an onset of clinical symptoms observed before the age of 5 yrs. All subjects were on a continuous corticosteroid regimen (deflazacort $n = 55$; prednisone $n = 22$), able to walk 100 meters, and climb four stairs. Patients were excluded if they reported any other medical condition that could affect their muscle function or overall functional performance. Subjects were tested for muscle strength and functional ability at 3 time points (baseline, 1 yr, and 2 yrs). The study was approved by the institutional review boards at each of the 3 participating, *ImagingDMD* sites (University of Florida, The Children's Hospital of Philadelphia, and Oregon Health Science University). At the start of the study, written informed consent was obtained from a parent or legal guardian, and written assent was obtained from each subject.

At each time point, the subjects' age, height, and body weight were recorded. In addition, KE and PF isometric peak torque (PT) was measured using the isometric mode of a computerized isokinetic dynamometer (Biodex, System 3.0, Biodex Corp, Shirley, NY). Functional ability was assessed using the following four timed performance tests: the 10 m walk/run,[1,5] supine to stand (STS),[14,15] four stairs climb,[1,5] and six-min walk test (6MWT).[16] For the first three timed tests, up to three trials were performed, and the fastest time to complete the task was recorded. If a subject was unable to complete the task within 45 secs or without assistance, the subject was considered to have lost the ability to perform that test.

Isometric Muscle Strength Testing

Subjects were seated in the Biodex dynamometer chair. Knee extensor strength testing was performed with the right knee and hip positioned at 90 degrees of flexion.[1,15] For PF strength testing, a custom made platform was used, with the knee placed at approximately 20–30 degrees of flexion, whereas the ankle was placed in a neutral position (0 degrees of plantar flexion).[1,15] For both KE and PF testing, the subject was asked to push against a static pad and maintain a maximal isometric force for approximately 5 secs, followed by a rest period of 1 min before the next trial. Subjects performed a minimum of five trials; in the event that the last trial's torque output exceeded all of the previous trials, the subject was asked to perform additional trials until there was a decrement or plateau in force production. The highest absolute PT value in foot-pound (ftlb) was calculated for both KEs (KE_{PT}) and PFs (PF_{PT}). Because there is a great amount of variability in body size with age, both KE and PF PTs were normalized to body surface area (BSA)[1,17,18] using the formula hereinafter. Normalized torque (PTBSA) for both KEs (KE_{PTBSA}) and PFs (PF_{PTBSA}) was also used for analysis.

$$\text{BSA } (m^2) = \sqrt{(\text{height (cm)} \times \text{weight (kg)}/3600)}^{17}$$

Functional Testing

To examine the functional ability of subjects with DMD, the participants were asked to perform four timed performance tasks in the following order: 10m walk/run, six-min walk, four stairs climb, and STS. Subjects performed each timed functional task, except for the 6MWT, three times, and the fastest time was used for analysis. Subjects were given an adequate break between the tasks to minimize the effect of fatigue.[19]

Statistical Analysis

To examine the longitudinal progression in both absolute and normalized PT for both KE and PF, a multivariate regression analysis was used with time as the covariate (using SAS proc mixed, (2015) SAS Institute Inc, Cary, NC). This approach assumes that the missing data are ignorable (missing at random). To further examine the effect of age on disease progression, subjects were divided into the following four age groups: 5–6.9 yrs, 7–8.9 yrs, 9–10.9 yrs, and 11+ yrs. Subjects who were no longer able to perform timed performance tasks were assigned values higher than the most rapidly progressing ambulatory child, and the lowest value was assigned for the 6MWT. We subsequently used rank based approaches that are invariant to the actual value used. For timed performance measures not available because of missing time points, we imputed them using a multivariate normal imputation approach (using the R package norm R Core Team (2012), R: A language and environment for statistical computing, R Foundation for Statistical Computing, Vienna, Austria). Because subjects who were no longer able to perform functional tasks were assigned values, Spearman correlation coefficients (rank based) were used to determine the relationship between strength and functional abilities at baseline. This method was also used to determine the relationship over time, but for this analysis, we did not include those who lost the ability to complete the "timed performance tests as just filling in the 'extreme' value as we did for baseline does not work in a longitudinal setting." Area under the receiver operating characteristic curve was used to determine the ability of strength in PF and KE to predict loss

TABLE 1. Baseline characteristics and demographics of control group and DMD subjects

		DMD			
	Control	All	5–6.9 yrs	7–8.9 yrs	9–10.9 yrs	11+ yrs
n	46	77	18	24	19	16
Age, yr	9.2 ± 2.2	8.9 ± 2.1	6.4 ± 0.5	8.1 ± 0.5	9.9 ± 0.6	11.8 ± 0.9
Body weight, kg	33.3 ± 12.4	29.5 ± 10.4	21.4 ± 3.6	26.5 ± 9.2	29.9 ± 6.3	42.1 ± 8.6
Height, cm	137.5 ± 12.3	121.4 ± 16.6	111.2 ± 5.5	120.7 ± 25.3	123.3 ± 6.4	131.5 ± 7.4
BSA, kg/cm^2	1.1 ± 0.3	1.0 ± 0.2	0.8 ± 0.1	0.9 ± 0.1	1.0 ± 0.1	1.2 ± 0.2

of ability in performing timed functional tasks. The level of significance for all the analysis was set at α value of 0.05. Data are presented as mean ± SE, unless otherwise stated.

RESULTS

Subjects Demographics

The demographics of subjects with DMD (n = 77) who completed the 2-yr study and age-matched controls (n = 46), studied at a single time point, are provided in Table 1. The Lower Extremity Brooks score in patients with DMD ranged from 1 to 3.

Cross-sectional Comparison of Lower Limb Strength in DMD and Age-Matched Healthy Controls

Both KE and PF PT were significantly lower in DMD patients compared with controls ($P < 0.0001$). At baseline, a five-fold difference was found in KE_{PT} (DMD = 11.8 ± 0.8 ftlb, control = 58.4 ± 4.8 ftlb) and a two-fold difference in PF_{PT} (DMD = 25.9 ± 1.0 ftlb, control = 59.6 ± 3.6 ftlb). A similar pattern was found when normalizing PT to body surface area, with both KE_{PTBSA} and PF_{PTBSA} showing significantly lower ($P < 0.0001$) values in DMD (KE_{PTBSA} = 12.3 ± 0.9 ftlb/cm^2; PF_{PTBSA} = 26.2 ± 0.8 ftlb/cm^2) in comparison with controls (KE_{PTBSA} = 49.5 ± 2.5 ftlb/cm^2; PF_{PTBSA} = 51.6 ± 2.1 ftlb/cm^2).

Stratification of the control healthy and DMD subjects by age showed a progressive increase in both absolute and normalized torque with age in control healthy subjects. In contrast, DMD subjects showed a trend toward increase in $PF_{PT,}$ but not $KE_{PT,}$ and both muscle groups when normalized to BSA showed a decline in force production with age (Table 2). This resulted in a widening of the gap between controls and DMD with age, with a 10-fold difference in KE_{PTBSA} in the oldest age group (11–14 yrs).

Longitudinal Changes in Lower Limb Strength

In subjects with DMD, $KE_{PT,}$ but not $PF_{PT,}$ showed a significant but small decline for 2 yrs. However, when strength was normalized to BSA (KE_{PTBSA} and PF_{PTBSA}), both muscle groups showed a significant decline for 2 yrs at $P < 0.001$ and $P < 0.01$, respectively (Table 3).

When we examined the change in strength for 2 yrs in the different age groups, a significant decline in absolute PT (KE_{PT} and PF_{PT}) was found in the 7- to 8.9-yr age group, but not in the other age groups (Fig. 1). When strength was normalized to BSA, a significant decline in both KE_{PTBSA} and PF_{PTBSA} was found in the 7- to 8.9-yr and 9- to 10.9-yr age group (Fig. 1).

Relationship Between Strength and Performance on Timed Functional Tests

At baseline, both absolute and normalized torque in the KE showed a significant correlation with performance on the functional tests, with stronger correlations observed with the shorter timed tests (r = 0.56–0.71) then the 6MWT (r = 0.34–0.38) (Table 4). Absolute PT production in the PF did not show a significant correlation with any of the timed tests, but normalized PF_{PTBSA} demonstrated a modest correlation with all functional tests (r = 0.27–0.38).

When examining the relationship between 2-yr changes in strength and performance on timed functional tasks, significant

TABLE 2. Baseline comparison of muscle strength for KEs and PFs among different age groups for healthy control and DMD subjects

	KE_{PT}		KE_{PTBSA}		PF_{PT}		PF_{PTBSA}	
	Control	DMD	Control	DMD	Control	DMD	Control	DMD
5–6.9 yrs	26.6 ± 2.5, *n* = 10	14.3 ± 1.3, *n* = 18	35.8 ± 5.8, *n* = 10	17.6 ± 1.6, *n* = 18	30.2 ± 2.1, *n* = 10	22.2 ± 1.3, *n* = 18	39.3 ± 4.3, *n* = 10	27.2 ± 1.2, *n* = 18
7–8.9 yrs	44.5 ± 2.3, *n* = 14	11.3 ± 1.6, *n* = 24	51.0 ± 2.9, *n* = 14	12.1 ± 1.6, *n* = 24	43.8 ± 2.2, *n* = 14	26.1 ± 1.4, *n* = 24	50.1 ± 1.4, *n* = 14	27.2 ± 1.3, *n* = 24
9–10.9 yrs	69.9 ± 5.7, *n* = 13	10.7 ± 1.5, *n* = 19	68.8 ± 5.4, *n* = 13	10.9 ± 1.6, *n* = 19	57.1 ± 3.1, *n* = 13	24.8 ± 0.9, *n* = 19	57.3 ± 4.2, *n* = 13	24.9 ± 1.2, *n* = 19
11+ yrs	98.5 ± 13.6, *n* = 9	10.7 ± 1.8, *n* = 16	83.5 ± 7.8, *n* = 9	8.4 ± 1.3, *n* = 16	68.3 ± 6.0, *n* = 9	30.7 ± 3.7, *n* = 16	59.1 ± 4.0, *n* = 9	24.5 ± 2.5, *n* = 16

TABLE 3. Change of strength in DMD subjects for 2 yrs

	Absolute Torque (PT)			Normalized Torque (PTBSA)		
	Baseline	**Year 1 (%change)**	**Year 2 (%change)**	**Baseline**	**Year 1 (%change)**	**Year 2 (%change)**
KE	11.8 ± 0.8	11.5 ± 0.9 (−2.5%)	10.7 ± 0.9[a] (−9.3%)	12.3 ± 0.9	11.3 ± 0.9 (−8.1%)	9.9 ± 0.8[c] (−19.5%)
PF	25.9 ± 1.0	25.6 ± 1.1 (−1.2%)	25.0 ± 1.1 (−3.5%)	26.2 ± 0.8	24.3 ± 0.9 (−7.3%)	22.7 ± 1.0[b] (−13.4%)

[a]Significant at $P < 0.05$ from baseline.
[b]Significant at $P < 0.001$ from baseline.
[c]Significant at $P < 0.0001$ from baseline.

correlations were found with absolute and normalized strength in both muscle groups for specific tasks, but the strength of the correlations were weak, because none of the *r* values exceeded 0.34 (Table 4).

Strength as Predictor of Loss of Functional Ability

Using receiver operating characteristic curves, we estimated an optimal threshold and the associated sensitivity and specificity for each strength variable to predict loss of the ability to perform each of the four functional measures (Table 5). In general, normalized strength was a better predictor of loss of function than absolute strength. The best predictor was PF_{PTBSA} with relatively high sensitivity and specificity for all the functional measures, except STS.

DISCUSSION

To our knowledge, this is the first study to compare the longitudinal changes in KE and PF strength for 2 yrs, using quantitative strength testing measures in a large cohort of subjects with DMD. In boys aged 5 to 14 yrs, all taking corticosteroids, a significant decline in absolute KE strength, but not PF strength, were detected. However, when normalizing strength to BSA, to compensate for changes in height and body weight, both muscle groups showed a significant decline in strength production. Cross-sectionally, baseline KE (both absolute and

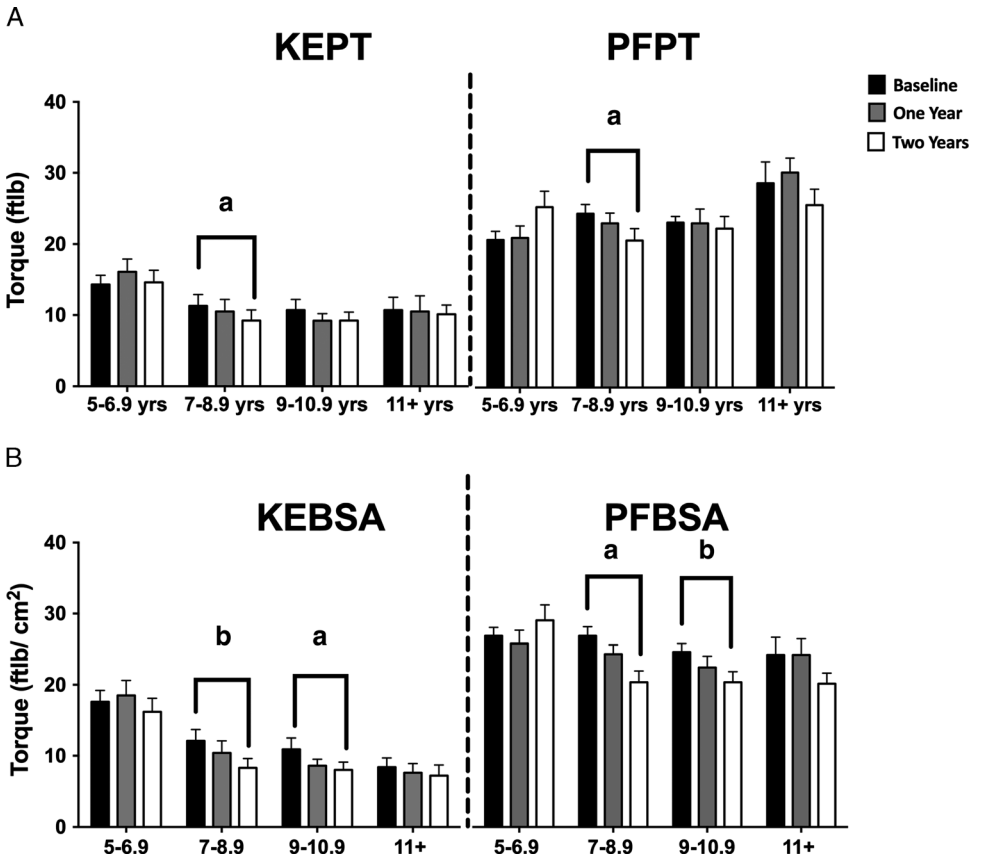

FIGURE 1. A, Longitudinal alteration in absolute KE and PF PT. B, Normalized PF and KE PT by age group. [a]Significant different at $P < 0.05$. [b]Significantly different at $P < 0.001$.

TABLE 4. Spearman correlation between strength and function at baseline, and Δ muscle strength (absolute and normalized) and Δ functional ability (as measured by timed functional tasks) in DMD subjects for 2 yrs

	Absolute Torque (PT)						Normalized Torque (PTBSA)					
	Baseline		Baseline to 1 yr		Baseline to 2 yr		Baseline		Baseline to 1 yr		Baseline to 2 yr	
	KE_{PT}	PF_{PT}	KE_{PT}	PF_{PT}	KE_{PT}	PF_{PT}	KE_{BSA}	PF_{BSA}	KE_{BSA}	PF_{BSA}	KE_{BSA}	PF_{BSA}
10-m walk/run	**−0.56**[c]	−0.09	**−0.24**[b]	−0.20	**−0.23**[b]	**−0.32**[a]	**−0.64**[c]	**−0.38**[b]	**−0.23**[b]	−0.21	**−0.16**[a]	**−0.33**[a]
STS	**−0.60**[c]	−0.07	**−0.24**[a]	−0.04	**−0.17**[a]	−0.25	**−0.71**[c]	**−0.33**[b]	**−0.22**[a]	−0.03	**−0.15**[a]	−0.29
Six-min walk	**0.34**[b]	0.18	**0.19**[a]	0.08	**0.16**[a]	0.30	**0.38**[c]	**0.27**[a]	**0.22**[a]	0.10	0.12	**0.34**[a]
Four stairs climb	**−0.62**[c]	−0.03	−0.12	−0.03	**−0.26**[b]	−0.19	**−0.69**[c]	**−0.28**[b]	−0.13	−0.04	**−0.22**[b]	−0.22

[a]Significant at $P < 0.05$.
[b]Significant at $P < 0.01$.
[c]Significant at $P < 0.001$.

normalized) showed a strong correlation with performance on the ambulatory functional tests. However, the correlation between both longitudinal changes in KE and PF strength and changes in performance on functional tests was modest. Using receiver operating characteristic curves, PF strength was found to be a stronger predictor of *loss* in the ability the complete the different timed performance tasks across 2 yrs, except for the ability to get up from supine.

The antigravity KEs and ankle PFs were selected for investigation as these two muscle groups have been shown to play a significant role in daily functions such as standing, walking, stair climbing, and getting up from the floor.[20,21] Both muscle groups are also well-known to display atrophy or muscle wasting in a variety of conditions associated with inactivity. Recent, magnetic resonance imaging studies in DMD have demonstrated significant atrophy, fatty infiltration, and muscle pathology in the rectus femoris and vasti muscles, responsible for knee extension.[22] The soleus and gastrocnemius muscles on the other hand typically display muscle hypertrophy, before the replacement of muscle by intramuscular fat.[23] Finally, KE muscle strength has been used in a number of clinical trials as a functional end point. Fewer clinical trials have included PF, presumably because of the difficulty in reliably measuring this muscle group using manual muscle testing and quantitative myometry. For this purpose, we used an isokinetic dynometer and a custom designed platform.

Strength normalized to BSA was found to be more sensitive to disease progression than absolute strength. Previous studies in pediatric populations have shown the importance of reporting normalized data, as changes in height and weight with growth and normal development can act as confounding factors.[24] Subjects with DMD demonstrated a decline in both normalized KE and PF for 2 yrs, whereas healthy subjects displayed an increase in normalized strength with age, widening the gap between both populations. These results support earlier pilot findings from our laboratory (2010).[1] Other factors, beyond disease pathology, such as delayed onset of puberty and stocky stature with corticosteroid use may also contribute to increasing gap with age.

No significant decline in lower limb strength was observed for 2 yrs in a boy with DMD in the youngest age group (5–6.9 yrs). This might be due to the fact that gains in muscle

TABLE 5. Receiver operating characteristic curve estimates to assess muscle strength (absolute and normalized) as a predictor of loss of functional ability on timed performance tasks

Strength Variable	Function Variable	Threshold	Sensitivity	Specificity	Area Under Curve	95% CI (UL–LL)
KE, ftlb	10-m walk/run	6.8	70.1	87.0	0.78	0.68–0.87
	4 stairs	6.7	71.9	84.5	0.81	0.72–0.88
	6MWT	6.9	83.3	65.7	0.75	0.65–0.85
	STS	7.5	74.7	78.3	0.78	0.68–0.87
PF, ftlb	10-m walk/run	18.3	82.7	68.6	0.73	0.56–0.88
	4 stairs	19.4	80.3	68.6	0.74	0.59–0.86
	6MWT	17.9	83.4	66.8	0.73	0.55–0.87
	STS	23.1	63.4	54.2	0.58	0.46–0.69
Normalized KE, ftlb/cm^2	10-m walk/run	5.8	73.0	87.0	0.81	0.72–0.90
	4 stairs	5.7	76.0	86.6	0.85	0.77–0.91
	6MWT	5.9	71.9	81.7	0.79	0.71–0.87
	STS	6.6	77.6	75.1	0.83	0.75–0.90
Normalized PF, ftlb/cm^2	10-m walk/run	18.1	83.6	85.6	0.87	0.77–0.95
	4 stairs	18.8	83.5	87.4	0.87	0.78–0.94
	6MWT	18.1	83.3	87.8	0.87	0.77–0.95
	STS	22.1	72.5	70.6	0.75	0.67–0.82

strength with normal growth and development in this age group out way the effect of disease pathology on muscle. In general, a decline in muscle strength was seen approximately 7 yrs of age. These findings are consistent with results reported by Lerario et al. (2012)[10] who examined the KEs and found deterioration in strength starting at a mean age of 7.5 yrs. In contrast, McDonald et al. (1995)[5] reported a decline in subjects aged 4–6 yrs. This difference may be attributed to an improvement in care. All the subjects enrolled in our study were taking corticosteroids, which has been shown to improve force production and functional ability in ambulatory subjects with DMD.[12,25] Although McDonald et al. (1995)[7] did not specifically report the corticosteroid use in his subject population, the study was performed in the 90s when corticosteroids was not considered standard of care.

Although corticosteroid treatment is considered the standard of care in DMD and has been associated with improvements in muscle strength and a delay of loss of ambulation, it does have some adverse effects. Common reported adverse effects include weight gain, Cushingoid, loss of bone mass, and behavioral deficits.[25,26] Presently, new drugs are under development that strive to provide some of the same positive effects, such as reduction in inflammation, while minimizing the adverse effects typically associated with corticosteroid use.[26,27]

Evaluating the Relationship Between Strength and Function Longitudinally

The ability to perform ambulatory timed tasks was more strongly correlated to strength in the proximal KE group compared with the distal PF group. These findings indicate that these timed performance tasks, commonly used in clinical trials, are more dependent on proximal muscle strength. Of all the timed functional performance tests, 6MWT showed the weakest correlation with muscle strength. Although the 6MWT is well accepted by the U.S. Food and Drug Administration as a primary outcome measures, it may not directly assess lower limb muscle performance. The 6MWT was initially developed as cardiopulmonary assessment test and has been criticized for its potential dependence on motivation, especially in a pediatric population. However, given the limited number of clinically relevant outcome measures available, it remains a valuable end point in clinical trials targeting ambulatory DMD patients.

Despite a strong cross-sectional relationship between KE strength and performance on timed functional tasks, only a modest correlation was found between change in strength and change in function for 2 yrs. Similarly, Beenaker et al. (2005)[14] reported that the declines in strength and loss of functional ability do not mirror one another. These findings emphasize that a decrease in functional ability is not solely dependent on strength of the lower limbs; other factors such as strength of the trunk musculature,[28] compensatory strategies,[28,29] and contractures[30] may play an important role. Interestingly, PF strength was a relatively better predictor of loss of the ability to perform all functional tasks, except for STS. Based on these findings, we speculate that patients with extensive involvement of the KEs can potentially still complete ambulatory tests, and only after significant decline in PF strength, do they lose the ability to perform the test altogether.

This study provides an account of changes in proximal and distal lower limb strength in a large cohort of subjects with DMD over a period of 2 yrs and examines the relationship with decline in performance on timed functional tests. Our findings support the concept that change in lower limb strength alone does not account for the decline in functional ability in DMD. Based on these findings future studies should examine how changes in other factors, such as neural drive, strength of postural muscles, and compensatory strategies affect overall functional ability in this patient population.

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